SDHA gain-of-function engages inflammatory mitochondrial retrograde signaling via KEAP1-Nrf2

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Whether screening the metabolic activity of immune cells facilitates discovery of molecular pathology remains unknown. Here we prospectively screened the extracellular acidification rate as a measure of glycolysis and the oxygen consumption rate as a measure of mitochondrial respiration in B cells from patients with primary antibody deficiency. The highest oxygen consumption rate values were detected in three study participants with persistent polyclonal B cell lymphocytosis (PPBL). Exome sequencing identified germline mutations in SDHA, which encodes succinate dehydrogenase subunit A, in all three patients with PPBL. SDHA gain-of-function led to an accumulation of fumarate in PPBL B cells, which engaged the KEAP1-Nrf2 system to drive the transcription of genes encoding inflammatory cytokines. In a single patient trial, blocking the activity of the cytokine interleukin-6 in vivo prevented systemic inflammation and ameliorated clinical disease. Overall, our study has identified pathological mitochondrial retrograde signaling as a disease modifier in primary antibody deficiency.

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